Reviewer #1:
Scientific Quality: Grade C (Good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Minor revision
Specific Comments to Authors: The author reports an evidence review of postoperative radiotherapy in resected non-small cell lung cancer. **I have few comments.**

- The Lung ART trial (NCT00410683) is the most important study to date in evaluating PORT. Therefore, the author should provide a more detailed overview of this study. In particular, please add that the candidate of the study is patients with stage III pN2 disease. Doesn't the result of this study determine that PORT is not recommended for patients with complete resected (R0) stage III NSCLC? If it cannot be determined, what was missing from this trial.

ANSWER:

The long-awaited preliminary results of the Lung ART trial (NCT00410683)8, which included patients with NSCLC who underwent complete resection with adjuvant ChT, were recently presented at the ESMO 2020 meeting. Lung ART is a multi-institutional randomized phase III trial which included stage III N2 NSCLC cases comparing mediastinal PORT (54 Gy/27-30 fractions) to no PORT in very selected patients: PS 0-2, complete resection with optimal nodal exploration and proven N2 disease.

The main endpoint was disease-free survival (DFS). Between August 2007 and July 2018, 501 patients were randomized after surgery or after ChT: 252 patients allocated to PORT, and 249 to no PORT. With a median FU of 4.8 years DFS HR was 0.85 (95%CI [0.67-1.07]); median DFS was 30.5 months with PORT [24-48] and 22.8 without PORT [17-37]; 3-year DFS was 47.1% with PORT vs 43.8% without PORT (p=ns), and finally, 3-year OS was 66.5% with PORT vs 68.5% without PORT (p=ns). Early and late Gr 3-5 cardio-pulmonary toxicity was respectively 7 and 20% in PORT arm vs 3,2 and 7,7 % in control arm. Nonetheless, PORT significantly decreased LRR in the mediastinum (46.1% vs. 25% with and without PORT, respectively), a finding that suggests that PORT could offer a clinical benefit in a well-selected subgroup of patients.

However, these preliminary results raised further doubts about the role of PORT in NSCLC. The findings of this landmark trial are extremely important and may come to redefine the role of radiotherapy in NSCLC. According to these data, PORT should not be routinely recommended to all resected stage III N2 NSCLC patients.

The decision to prescribe o not PORT must be individualised according to the patient's specific characteristics. In general, PORT should be indicated only in highly selected patients with good performance status (PS 0-1), significant mediastinal lymph node involvement (pN2, extracapsular extension), and/or residual disease (R1-R2) after surgery. In addition, PORT must be only performed in cases with a favourable dose distribution that fulfils the dose restriction criteria for the organs of risk (OARs), especially cardiopulmonary restrictions.

- In addition, aren't all of the guidelines the author had presented in the text before the results of this trial were available? I think the author needs to discuss whether or not the results of this study may change the guidelines.

ANSWER:

At the time of writing this manuscript, the recommendations exposed in Table 1 faithfully reflect what is reflected in the main international guidelines, emphasizing that both ASCO and ESMO (prepared mainly by medical oncology) leave the possibility of evaluating PORT only in some selected pN2 cases, and they reject the use of postoperative radiotherapy in all cases with optimal R0 complete resection.

- The author describes the imaging of mediastinal lymph nodes in Section 4. However, the theme of this review is postoperative radiotherapy. Since mediastinal lymph nodes can basically be evaluated using surgical specimens, I think it is unnecessary to describe about diagnostic imaging.

ANSWER:

We have decided to include some clinical-radiological basic aspects about diagnostic management in our manuscript, because of it´s essential to know how to obtain histological or cytological confirmation of the existence of mediastinal disease in cases with high-risk images, since this data will be crucial in taking of subsequent decisions for the global therapeutic management of patients. In the LUNG ART study itself, it is required that those patients receiving neoadjuvant chemotherapy have histological or cytological confirmation of N2 involvement in order to enter the trial.

- The author shows the recommended PORT doses for R0 and R1/2 in Section 6. However, the rationale for recommendation is not cited or explained.

ANSWER:

In completed-resected (R0) surgeries, the recommended dose is 50-54 Gy using a conventional fractionation scheme (1.8-2 Gy/day)53. However, in high-risk patients with R1 or R2 margins, the total dose may be increased up to 54-60 Gy, or even up to radical doses of 60-66 Gy if there is evidence of macroscopic residue in the surgical bed or mediastinal region.

We have added a new cite for explain it:

53. Corso CD, Rutter CE, Wilson LD, Kim AW, Decker RH, Husain ZA. Re-evaluation of the role of postoperative radiotherapy and the impact of radiation dose for non-small-cell lung cancer using the National Cancer Database. J Thorac Oncol. 2015 Jan;10(1):148-55. doi: 10.1097/JTO.0000000000000406. PubMed PMID: 25325781.

- The phase III trial have demonstrated the efficacy of atezolizumab, an immune checkpoint inhibitor, as adjuvant therapy for resected NSCLC, and adjuvant therapy using atezolizumab is expected to become one of the standard treatments for patients with resected NSCLC in the near future. Please add a discussion on the position of PORT in the coming ear of immunotherapy.

ANSWER:

Even though check-point inhibitors, such as atezolizumab, are showing great efficacy in the treatment of non-small cell lung cancer, to date, there is not enough solid evidence for their generalized indication in the segment postoperative adjuvant. There are some studies that are exploiting this possibility, such as IMpower010 trial, a multicenter open-label, randomized trial (NCT02486718), however, we lack mature results in this regard.

Furthermore, the objective of our review article was not to deepen into the indications for pharmacological treatment, but rather to study what solid and real evidence exists for the use of PORT in patients with non-small cell lung cancer, in which cases it can be avoided, what poor prognostic factors can lead to recommend it and what technical aspects should be improved to significantly reduce the long-term cardiotoxicity that appears in published studies.

(1) ***Science editor:*** 1 Scientific quality: According to the cover letter, the authors submitted this manuscript as an editorial article. I am not sure this is the appropriate format: this manuscript is more consistent with a minireview on a very specific topic, namely Postoperative radiotherapy (PORT) in resected non-small cell lung cancer (NSCLC). The topic is within the scope of the WJCO.

(1) Classification: Grade C; (2) Summary of the Peer-Review Report: There are several specific comments to the author:

i) The Lung ART trial (NCT00410683) is the most important study to date in evaluating PORT. Therefore, the author should provide a more detailed overview of this study. In particular, please add that the candidate of the study is patients with stage III pN2 disease.
ANSWERED ABOVE

ii) Doesn't the result of this study determine that PORT is not recommended for patients with complete resected (R0) stage III NSCLC? If it cannot be determined, what was missing from this trial. In addition, aren't all of the guidelines the author had presented in the text before the results of this trial were available? I think the author needs to discuss whether or not the results of this study may change the guidelines.
ANSWERED ABOVE

iii) The author describes the imaging of mediastinal lymph nodes in Section 4. However, the theme of this review is postoperative radiotherapy. Since mediastinal lymph nodes can basically be evaluated using surgical specimens, I think it is unnecessary to describe about diagnostic imaging.
ANSWERED ABOVE

iv)The author shows the recommended PORT doses for R0 and R1/2 in Section 6. However, the rationale for recommendation is not cited or explained.
ANSWERED ABOVE

v) The phase III trial have demonstrated the efficacy of atezolizumab, an immune checkpoint inhibitor, as adjuvant therapy for resected NSCLC, and adjuvant therapy using atezolizumab is expected to become one of the standard treatments for patients with resected NSCLC in the near future. Please add a discussion on the position of PORT in the coming ear of immunotherapy.
ANSWERED ABOVE

(3) Format: There are 3 tables. Table 2 and Table 3 should be completed with references and links, respectively. The manuscript is not consistent with the editorial instructions of the journal, overall. The references are not appropriately formatted.
REFERENCES CHANGED AND LINKS ADDED

(4) References: A total of 58 references are cited, including 17 references published in the last 3 years; as said, the format of references is not completely/always consistent with the journal policy.
REFERENCES CORRECTED

(5) Self-cited references: There are no self-citations.

2 Language evaluation: Classification: Grade B.

3 Academic norms and rules: The authors need to provide the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement. No academic misconduct was found in the Bing search.
CONFLICT OF INTEREST DISCLOSURE ADDED

4 Supplementary comments: to clarify the article type and if it is an invited or unsolicited manuscript.
DONE

5 Issues raised:
- to reconsider the manuscript type (the author registered it as an Evidence Review, but he presented it as an Editorial in the cover letter) and revise the content accordingly.
REVIEW

- to clarify if this is an invited manuscript (as stated in the cover letter) or an unsolicited manuscript, as indicated in the editorial system at the submission
INVITED MANUSCRIPT

- to use the appropriate manuscript template (according to the editorial rules and the article type)
DONE

- to format all the citations and references according to the editorial rules of the journal
DONE

- to address all the specific comments raised by the reviewer
DONE

- to provide a clear introduction, where the author can also highlight the aim and novelty of their scientific contribution
DONE

6 Re-Review: Required.

7 Recommendation: Potential Acceptance (Reconsider after author's revision)

(2) ***Company editor-in-chief:*** I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Clinical Oncology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.

COVER LETTER CORRECTED

14th April 2021

Prof. Hiten R.H. Patel, MD, PhD
Prof. Stephen Safe, PhD
Editors-in-Chief
World Journal of Clinical Oncology

Dear Prof. Hiten, R.H. Patel and Prof. Stephen Safe,

First, we want to thank you for your gentle invitation to publish in WJCO. The invitation number is 03428837.

Please find enclosed our manuscript entitled "***Postoperative radiotherapy (PORT) in resected non-small cell lung cancer (NSCLC): the never-ending story"***, which we submit for consideration as an **Evidence Review**.

We believe that readers of **World Journal of Clinical Oncology** will be interested in this manuscript. The present clinical evidence review were developed by Spanish radiation oncologists on behalf of the Oncologic Group for the Study of Lung Cancer/Spanish Society of Radiation Oncology (GOECP/SEOR) to provide a current review of the diagnosis, planning, and postoperative treatment of resected NSCLC. These guidelines emphasise the current evidence, risk factors, indications as well as treatment fields, radiation techniques, and fractionation.

We have no conflicts of interest to disclose.

We confirm that this work is original and has not been published previously, nor is it currently under consideration for publication elsewhere.

We confirm that the manuscript has been read and approved for submission by all the named authors.

Yours sincerely,

Javier Serrano, MD, PhD

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MANUSCRIPT CORRECTED

Postoperative radiotherapy (PORT) in resected non-small cell lung cancer (NSCLC): the never-ending story

1. Historical evolution of PORT

One of the great historical controversies in the field of thoracic oncology is the use of PORT in patients with NSCLC. The rationale for this therapeutic strategy is the high risk of locoregional recurrence (LRR) after radical surgery, especially in patients with pN2 disease, who account for up to 30% of patients. The development of LRR in patients with NSCLC has important clinical implications and is associated with worse survival outcomes[1]. Several different pathological variables have been associated with a higher risk of developing LRR, including tumour size > 3 cm, lymphovascular invasion, visceral pleural invasion, and involvement of multiple lymph nodes[2].

The role of PORT in NSCLC remains controversial, mainly because studies carried out over the last few decades have reported conflicting safety and efficacy results. Although multiple retrospective and prospective studies have been performed, we still lack high-quality evidence to confirm or definitively rule out PORT in these patients. A meta-analysis published in 1998 found that PORT was associated with lower overall survival (OS) rates in patients with stage I-II disease, with 2-year OS rates of 43% in the non-PORT group versus 30% in the patients that received PORT, although there was no clear evidence that PORT negatively influenced outcomes in patients with stage III pN2 disease[3]. In older studies, the poor outcomes of PORT could be due to the high levels of morbidity and mortality associated with obsolete radiotherapy techniques or inappropriate doses, fractionations, and/or irradiation volumes. In fact, a more recent meta-analysis demonstrated that PORT improves OS outcomes when modern technology (linear accelerators vs. cobalt therapy units) is used to deliver the radiation dose[4].

Despite the contradictory findings described above, several studies have reported a clear benefit for PORT in patients with involved lymph nodes (pN2) in terms of improved local control and even OS[5-7]. Among those studies with positive findings, the most important is the study carried out by Mikell et al.[7], who evaluated 2,115 patients with pN2 NSCLC based on data retrieved from the National Cancer Database (NCBD). In that study, PORT was associated with a significant increase in OS (42 vs. 38 months, p=0.048) in patients treated according to the therapeutic standards of the modern era (three-dimensional conformal radiotherapy [3D-CRT], adjuvant chemotherapy [ChT], etc.)[7].

The long-awaited preliminary results of the Lung ART trial (NCT00410683)[8], which included patients with NSCLC who underwent complete resection with adjuvant ChT, were recently presented at the ESMO 2020 meeting. Lung ART is a multi-institutional randomized phase III trial which included stage III N2 NSCLC cases comparing mediastinal PORT (54 Gy/27-30 fractions) to no PORT in very selected patients: PS 0-2, complete resection with optimal nodal exploration and proven N2 disease. The main endpoint was disease-free survival (DFS). Between August 2007 and July 2018, 501 patients were randomized after surgery or after ChT: 252 patients allocated to PORT, and 249 to no PORT. With a median FU of 4.8 years DFS HR was 0.85 (95%CI [0.67-1.07]); median DFS was 30.5 months with PORT [24-48] and 22.8 without PORT [17-37]; 3-year DFS was 47.1% with PORT vs 43.8% without PORT (p=ns), and finally, 3-year OS was 66.5% with PORT vs 68.5% without PORT (p=ns). Early and late Gr

3-5 cardio-pulmonary toxicity was respectively 7 and 20% in PORT arm vs 3,2 and 7,7 % in control arm. Nonetheless, PORT significantly decreased LRR in the mediastinum (46.1% vs. 25% with and without PORT, respectively), a finding that suggests that PORT could offer a clinical benefit in a well-selected subgroup of patients.

However, these preliminary results raised further doubts about the role of PORT in NSCLC. The findings of this landmark trial are extremely important and may come to redefine the role of radiotherapy in NSCLC.
According to these data, PORT should not be routinely recommended to all resected stage III N2 NSCLC patients. The decision to prescribe o not PORT must be individualised according to the patient's specific characteristics. In general, PORT should be indicated only in highly selected patients with good performance status (PS 0-1), significant mediastinal lymph node involvement (pN2, extracapsular extension), and/or residual disease (R1-R2) after surgery. In addition, PORT must be only performed in cases with a favourable dose distribution that fulfils the dose restriction criteria for the organs of risk (OARs), especially cardiopulmonary restrictions.

2. Current evidence and recommendations for PORT

The role of PORT in the treatment of NSCLC remains controversial. Although this therapeutic strategy has been evaluated in numerous retrospective and prospective studies, robust evidence to definitively support the value of PORT is still lacking, as can be seen in the lack of consensus among the clinical guidelines published by the main international scientific societies [9-13].

Currently, the most widely accepted indication for PORT, with the most evidence, is for the treatment of residual disease (including extracapsular extension) after radical surgery. Most international guidelines recommend PORT in patients with involved surgical margins (R1-R2) at the surgical bed due to the high risk of recurrence in this region, with a recommended dose ranging from 54-60 Gy (1.8-2 Gy/fraction).[14]

By contrast, in patients with stage pN2 disease, the current evidence suggests that the treatment decision should be assessed on a case-by-case basis by a multidisciplinary team to determine if the patient would be likely to benefit from PORT. The treatment decision should consider several key clinical characteristics, including the number of mediastinal nodal stations involved (≥ 1), the patient's general physical condition (PS 0-1), and cardiopulmonary function. Table 1 summarizes the recommendations proposed by the main international guidelines.

Guidelines	Clinical scenario	Recommendation for PORT
NCCN[9]	Stage pN0-1	Not recommended
	Stage pN2, negative surgical margins (R0)	Sequential
	Microscopic or macroscopic surgical margins (R1-R2)	Concomitant (selected cases) or sequential
ASTRO[10]	Stage pN2	Sequential
	Microscopic or macroscopic surgical margins (R1-R2)	Concomitant (selected cases) or sequential
	ESTRO-ASTRO[11]	
	Multiple nodal stations involved	Sequential
	Extracapsular nodal extension	Sequential

ESMO[12]	Early stage (I-II) disease (R0)	Not recommended
	Positive margins or chest wall involvement (R1-R2)	Sequential
	Stage pN2	Only in selected cases
ASCO[13]	Early stage (I-II) disease (R0)	Not recommended
	Stage pN2	Only in selected cases

Table 1. Recommendations for PORT according to the main international guidelines

Abbreviations. NCCN: National Comprehensive Cancer Network; ASTRO: American Sociedad of Radiation Oncology; ESTRO: European Society for Radiotherapy & Oncology; ESMO: European Society for Medical Oncology; ASCO: American Society of Clinical Oncology.

3. Management of cases with involved surgical margins

The rate of incomplete resections (microscopic or macroscopic; R1-R2) after radical surgery for lung cancer ranges from 1-17%[15]. In these cases, the aim of PORT is to reduce the risk of local recurrence and improve OS. Although various clinical guidelines recommend salvage surgery in patients with positive surgical margins, this approach is not supported by robust data. Ghiribelli et al.[16] evaluated OS in a series of patients with incomplete resections (R1), finding that survival was not correlated with the type of infiltration, nodal involvement, or histological type. As a result, in patients with microscopic residual tumours, the authors recommended salvage surgery only in patients with early stage (I-II) disease; by contrast, the recommended treatment in stage III pN2 disease is adjuvant radiotherapy.

A study published in 2012 evaluated the efficacy and toxicity of PORT according to histological subtype in patients (n=41) with incompletely resected NSCLC[17]. Of the 41 patients, 23 had microscopic (R1) and 18 macroscopic (R2) residual disease. The histologic distribution was as follows: squamous cell carcinoma (SCC) (n=23), adenocarcinoma (14), and other histologies (4). The predominant progression pattern was distant disease, observed in 13% of patients with SCC and 64% of those with adenocarcinoma ($p < 0.01$). Survival rates at 5-years were as follows: OS, 56%; local control (LC), 63%; DFS, 37%; and metastasis-free survival (MFS), 49%. On the multivariate analysis, the only significant predictors of better survival (DFS and MFS) were SCC histology, stage N0-1, and R1 surgical margins. The authors concluded that, in patients with R1 margins, PORT provides good LC without severe toxicity, but systemic therapy should always be considered due to the high risk of distant metastasis.

Hancock et al.[18] evaluated 3,102 surgically treated NSCLC patients included in the NCDB registry. Of these, 1688 had microscopically positive margins (R1). The authors compared patients according to margin status (R1 vs. R0), with significantly lower 5-year OS rates in the R1 group for all stages: stage I, 37% vs. 62% ($p < 0.0001$); stage II, 29% vs. 41% ($p < 0.0001$); and stage III, 19% vs. 33% ($p < 0.0001$). Administration of adjuvant ChT with PORT in the R1 group was associated with better OS than surgery alone, regardless of stage (stage I, 44% vs. 35%, $p=0.05$; stage II, 33% vs. 21%, $p=0.0013$; stage III, 30% vs. 12%, $p < 0.0001$).

In a study published in 2015, Wang et al.[19] evaluated 3,395 patients with incompletely resected stage II-III NSCLC to determine the influence of PORT on survival outcomes, finding that PORT was associated with significantly better 5-year OS (32.4% vs. 23.7%). Radiation doses between 50-70 Gy

improved survival rates in the PORT group versus the non-PORT group. However, when higher doses (> 70 Gy) were administered, there were no between-group differences in OS. The authors of that study concluded that PORT improves OS in patients with incompletely resected stage II-III NSCLC and should therefore be considered as an adjuvant treatment. They also suggested that the radiation dose in patients with macroscopic residual disease (R2) should be the same as those used for radical radiotherapy (60-66 Gy).

4. Mediastinal staging

Preoperative mediastinal staging

The appropriate management of NSCLC depends on accurate mediastinal staging. Contrast-enhanced chest computed tomography (CT) is currently the diagnostic test of choice for preoperative mediastinal staging. On CT imaging, nodes with a short-axis diameter ≥ 1 cm are considered pathological[20]. In recent years, 18F-fluorodeoxyglucose (FDG) positron-emission tomography (PET)-CT has transformed lung cancer staging due to its greater sensitivity. However, PET-CT has some limitations in cases with small nodes (< 1 cm) and in certain histologies in which FDG uptake is limited. PET-CT also has a high false positive rate (20%-25%) in the presence of intercurrent infections and inflammatory processes. Consequently, histopathologic confirmation of mediastinal node involvement is usually required, especially when the therapeutic approach depends directly on the results of this assessment[21-23]. Histological confirmation can be omitted in certain patients with small (≤ 3 cm) peripheral tumours without radiological evidence of suspected mediastinal involvement.

Mediastinal nodes can be obtained endoscopically through endobronchial ultrasound (EBUS) and/or endoscopic ultrasound (EUS) guided puncture, or surgically, through mediastinoscopy or video-assisted thoracoscopy (VATS). Endobronchial ultrasound (EBUS/EUS) is usually the first step in evaluating suspected mediastinal node involvement[24-25]. These minimally invasive endoscopic techniques are usually preferred to surgical approaches due to their good sensitivity and specificity profile and relatively low risk of morbidity. If the sample is negative, not assessable, or insufficient (despite radiological suspicion), staging should be completed with invasive techniques, which have a higher negative predictive value (NPV). For many years, conventional mediastinoscopy was the main surgical staging technique, despite the technical limitations of this procedure for the study of the posterior and inferior mediastinum, in which either extended cervical mediastinoscopy or VATS is necessary[26].

Mediastinal restaging after neoadjuvant therapy

Mediastinal restaging after neoadjuvant therapy (ChT or ChT+RT) is controversial. Some patients with stage IIIA, low volume N2 disease are classified as potentially resectable and may benefit from neoadjuvant therapy, which could increase the likelihood of achieving a complete response (CR) in the mediastinum, thus permitting surgical resection of the tumour[27]. In this clinical scenario, however, the value of CT for mediastinal restaging is questionable since CT-based assessment, although highly predictive of pathologic CR, tends to underestimate the true CR rate.

PET-CT is an excellent tool to assess the response of both the primary tumour and metastatic lesions, but it is less reliable in evaluating mediastinal involvement due to high rates of false negative and

false positives (20% and 25%, respectively)[28,29]. Therefore, histopathologic confirmation is necessary in cases with radiological response if surgical resection is being considered.

EBUS/EUS restaging after neoadjuvant therapy has a low sensitivity and a low NPV. If the test is negative, the surgical technique should be escalated to reduce the false negative rate[30]. Restaging via mediastinoscopy has a high sensitivity (> 60%), specificity (≈100%), positive predictive value (PPV; 100%) and NPV (> 73%); however, this procedure is not routinely performed due to its technical complexity in this clinical context. Rather, the recommended strategy is initial confirmation of stage N2 disease by EBUS or EUS-guided transbronchial aspiration during the initial workup, thus reserving mediastinoscopy for restaging[31].

5. Selection of candidates for PORT

Numerous studies have explored a wide range of prognostic factors potentially associated with an increased risk of LRR in order to identify high-risk patients suitable for adjuvant radiotherapy. In patients with NSCLC, the histological type is not currently considered a prognostic factor for adjuvant treatment due to the poor quality of the available data and contradictory findings in the literature. While some studies have found that SCC histology is associated with worse OS rates than adenocarcinoma[32,33], findings from other studies point in the opposite direction[34].

The findings of a recent meta-analysis involving 25,780 patients from 13 studies (most retrospective) underscored the prognostic value of multiple mediastinal node involvement. That study showed that, in patients with pN2 disease with ≥ one positive node and/or multiple N2 station involvement, PORT significantly improved both DFS (HR 0.57, 95% confidence interval [CI], 0.38–0.85) and OS (HR 0.85, 95% CI, 0.79–0.92)[35].

The lymph node ratio (LNR)—defined as the number of involved nodes divided by the total removed or examined—has also been significantly associated with survival outcomes. A recent study evaluated 11,341 patients with NSCLC and postoperative nodal involvement included the SEER (Surveillance, Epidemiology, and End Results Database) registry. The authors established three risk categories according to the LNR (LNR1 ≤ 0.28, LNR2 <0.81, and LNR3 > 0.81), finding that LNR3 was an independent prognostic factor for cancer-specific survival (CSS) (HR 2.54; 95% CI, 2.30–2.80; p<0.001)[36].

Other parameters, such as the positive and negative lymph node counts (PLN and NLN, respectively), have been developed to quantify the tumour load in mediastinal nodes. Zhou et al. reviewed data from 39,959 surgically-treated cases of NSCLC, demonstrating a significant association between mediastinal tumour burden and OS (PLN> 5; HR 2.0128, 95% CI, 1.6996–2.3836; NLN> 5; HR 0.7493, 95% CI, 0.7211–0.7785; LNR> 0.30; HR 1.7949, 95% CI,1.5329–2.1016); and with CSS (PLN> 5; HR 2.2147, 95% CI, 1.8095–2.7106; NLN> 5; HR 0.7214, 95% CI, 0.6869–0.7575; LNR> 0.30; HR 1.9627, 95% CI, 1.6219–2.3752)[37]. In this same line of research, another study evaluated 5,168 patients with stage IIIA-N2 NSCLC, finding that patients with PLN> 5 who underwent PORT had significantly better OS outcomes (HR 0.637, 95% CI, 0.518–0.784), a benefit that persisted even when compared to adjuvant ChT alone (HR 0.726, 95% CI, 0.564–0.934)[38].

The studies that have generated the most interest are those that have sought to stratify risk groups according to multiple clinical, pathologic, and molecular parameters. In this regard, the study by Deng

and colleagues[39] is worth highlighting. Those authors evaluated numerous characteristics—age, sex, surgical technique, histological type, degree of differentiation, tumour size, number of nodes evaluated (LNR index)—in a large sample (n=2,329) of patients included in the SEER database. Based on that analysis, the authors proposed a prognostic scoring model that classified patients into two risk categories (high and low), which was a significant predictor of survival outcomes (OS and CSS) [40].

Jiang et al. recently developed a model that incorporated several molecular biomarkers, together with other well-known clinical variables, to predict clinical outcomes in patients with stage IIIA pN2 NSCLC. In that study, the following variables were significantly associated with the risk of LRR: epidermal growth factor receptor (EGFR) status: wild-type vs. native (HR 3.666, 95% CI, 1.724-7.797); lymphocyte to monocyte ratio (LMR) < 4.69 (HR 2.364, 95% CI, 1.221-4.574); surgical procedure (VATS vs. thoracotomy) (HR 0.348, 95% CI, 0.175 -0.693); and pN2 LNR ≥ 38.9% (HR 3.597, 95% CI,1.832-7.062). The authors then used those data to develop a predictive model (Table 2) based on the four independent risk factors to determine the individual risk of LRR in each patient. This score, in turn, could be used to recommend or not adjuvant radiotherapy[41].

Risk model for LRR in stage pIIIA-N2 NSCLC		
Factor	**Category**	**Score**
EGFR status	Wild- type	**4**
LMR	LMR < 4.69	**2**
Type of surgery	Thoracotomy	**3**
LNR	LNR ≥ 38.9	**4**
Risk group	**Score**	**3-year LRFS**
Low risk	0 - 2	71.4%
Medium risk	3 - 5	57.3%
High risk	6 - 13	13.6%

Table 2. Proposed predictive model for locoregional recurrence in stage IIIA N2 NSCLC [41]
Abbreviations: LRFS, locoregional recurrence-free survival; LRR, locoregional recurrence; NSCLC; non-small cell lung cancer; LNR, lymph node ratio; LMR, lymphocyte-to-monocyte ratio.

6. Technical recommendations for the treatment of PORT

Simulation

The generally accepted recommendations provided by clinical guidelines for the management of NSCLC should be followed for positioning, immobilization, and treatment simulation. Systems designed to improve immobilization and control respiratory motion (4D-CT) should be used, preferably with image-guided radiotherapy (IGRT), to obtain smaller treatment volumes and more precise radiotherapy to achieve a better dosimetric distribution.

In general, CT imaging (slice thickness, 2-3 mm) should be performed with intravenous contrast to improve contouring of the nodal areas[42,43]. The use of 5FDG-PET-CT for postoperative simulation is not recommended due to the lack of robust data; moreover, interpretation of these images in the immediate postoperative period can be challenging due to the inflammation, which can lead to false

positives. Image interpretation after ChT is also difficult and it is easy to underestimate the residual disease (false negatives)[44].

Target volumes

The most important data for target volume definition were described in the Lung-ART clinical trial and based on contouring performed by 17 experienced thoracic radiation oncologists in two representative cases[45]. The clinical target volume (CTV) should include the bronchial stump, ipsilateral hilum, adjacent mediastinal pleura, and involved nodes (according to the pathology report). The involved nodal station and those immediately superior and inferior to that region should also be contoured, being careful to avoid oversizing the CTV. To generate the PTV (planning target volume), a margin of at least 0.5 cm in the mediolateral and dorsoventral directions (1 cm in the craniocaudal direction) should be applied to the CTV to minimize uncertainties related to tumour motion and patient positioning[46].

The definition of critical organs (OARs)[47] and dose restrictions are the same as in NSCLC, although with more restrictive lung criteria. In post-lobectomy patients, Boonyawan et al., proposed limiting the lung volume that receives 10 and 20 Gy (V10 and V20) to < 30% and <20%, respectively[48]. In patients older than age 65, the lung V5 should be reduced to ≤ 36%[49]; if IMRT is performed, the recommended V5 is < 64.9%, with mean lung dose (MLD) < 10.8 Gy[50]. In patients undergoing pneumonectomy, to ensure safety, these limitations should be even more restrictive, as follows: V5 <30%, V20 <13%, and MLD <7.5 Gy [51]. If 3D conformal radiotherapy (3D-CRT) is used, the V20 should be < 10%[52].

Dose and fractionation

In completed-resected (R0) surgeries, the recommended dose is 50-54 Gy using a conventional fractionation scheme (1.8-2 Gy/day)53. However, in high risk patients with R1 or R2 margins, the total dose may be increased up to 54-60 Gy, or even up to radical doses of 60-66 Gy if there is evidence of macroscopic residue in the surgical bed or mediastinal region.

The use of hypofractionated regimens is not advised due to the risk of increased toxicity. Currently, accelerated fractionation radiotherapy schemes (2 Gy/day, 7 days/week) are being explored (NCT02189967)[54].

In terms of treatment sequencing, PORT should be administered after completing ChT if the surgical resection is complete (R0); however, in patients with postoperative R1-R2 margins, there is some controversy surrounding the use of concomitant or sequential RT and ChT. As a result, the treatment sequence should be individualized based on the expected tolerance[55,56].

Although several radiotherapy techniques—3D-CRT, intensity modulated radiation therapy (IMRT), volumetric modulated arc therapy (VMAT), and tomotherapy—all provide optimal dosimetric results in the postoperative context[57], data from prospective studies support the routine use of the IMRT in NSCLC due to lower cardiac doses and a lower risk of severe pneumonitis.

7. Future lines of research in PORT

At present, there is broad consensus among radiation oncologists that the current level of evidence is insufficient to recommend PORT for all patients with stage III pN2 NSCLC, which is mainly attributable to the heterogeneous characteristics of patients with pN2 disease and treatment-related cardiopulmonary toxicity, which remains high despite efforts to reduce it.

In terms of the lack of homogeneity, it is evident that TNM staging in patients with pN2 NSCLC does not provide sufficient information to indicate or not adjuvant therapy. Consequently, it is essential to explore and evaluate new clinical, pathological, and molecular factors to better differentiate between different risk subpopulations, which would then allow us to tailor the treatment indication based on the patient's unique characteristics.

It is important to note that most of the prognostic factors identified to date have been derived from data obtained in large retrospective series or epidemiological records. Clearly, due to the important methodological limitations of those studies, it is difficult to extrapolate the findings of those studies into routine clinical practice without stronger supporting data. In this regard, new studies with more robust methodological designs are needed to obtain a higher level of evidence. Table 3 lists the main trials currently underway to evaluate PORT in NSCLC.

NCT	Title	Study Type	Link
NCT02977169	To Evaluate the Role of Postoperative Radiotherapy in Patients With IIIA(N2) Non-Small Cell Lung Cancer	Interventional	https://clinicaltrials.gov/ct2/show/NCT02977169
NCT02974426	To Evaluate the Optimal Timing of Postoperative Radiotherapy in Patients With IIIA(N2) Non-Small Cell Lung Cancer	Interventional	https://clinicaltrials.gov/ct2/show/NCT02974426
NCT04073745	Single Fraction Stereotactic Body Radiation Therapy After Surgery in Treating Patients with Non-small Cell Lung Cancer	Interventional	https://clinicaltrials.gov/ct2/show/NCT04073745
NCT03006575	Study of Split-course Chemoradiotherapy For Postoperative Locoregional Recurrence of Non-small Cell Lung Cancer	Interventional	https://clinicaltrials.gov/ct2/show/NCT03006575
NCT02555592	Strategy of Surgical Resection with Adjuvant Therapy for IIIA NSCLC and N2 Disease Only in Subaortic or Paraaortic Level	Observational	https://clinicaltrials.gov/ct2/show/NCT02555592
NCT02189967	Postoperative Radiotherapy of Non-small Cell Lung Cancer: Accelerated vs. Conventional Fractionation	Interventional	https://clinicaltrials.gov/ct2/show/NCT02189967
NCT00880971	Postoperative Radiotherapy for Patients with IIIA (N2) Non-small Cell Lung Cancer	Interventional	https://clinicaltrials.gov/ct2/show/NCT00880971
NCT01112631	Prospective Study of Quality of Life in Non-small Cell Lung Cancer (NSCLC) Patients Treated With/Without Postoperative Radiotherapy	Observational	https://clinicaltrials.gov/ct2/show/NCT01112631

Table 3. Registered active studies related to PORT.

The studies performed to date have consistently found an association between PORT and a higher risk of cardiopulmonary morbidity and mortality, a finding that undermines the clinical benefits of this treatment. However, some studies have shown that IMRT is superior to 3D-CRT in NSCLC in terms of dosimetry and survival outcomes[58]. Heavy particle therapy seems to show certain dosimetric advantages versus IMRT in terms of protection of OARs, and could significantly reduce cardiopulmonary toxicity, although prospective studies confirming this clinical benefit are not yet available[59].

For all the reasons described above, it is evident that only advanced radiotherapy techniques, such as VMAT or IMRT, which allow for better dose conformity, should be used for the treatment of NSCLC. In addition, these techniques should be used in all future clinical trials of PORT to better determine the true value of PORT in patients with NSCLC.

8. Conclusions

In patients with stage pN2 disease, current evidence suggests that the treatment decision should be evaluated on a case-by-case basis by a multidisciplinary team to determine whether the patient is likely to benefit from PORT. The treatment decision should consider several key clinical features, such as the volume of nodal mediastinal tumor burden, physical condition (performance status) and individual cardiopulmonary risk, but another technological issues, like availability to modern functional imaging devices or high dosimetric conformation radiotherapy (IGRT or VMAT), may be critical for a correct indication.

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